REMARKS

The Examiner rejected claims 1-14, 42, and 43, while withdrawing claims 15-41 and 44-59 from consideration. Claims 3, 15-30, and 51-59 are canceled herein without prejudice, claims 31-41 and 44-50 stand withdrawn, and new claim 60 is added. Thus, claims 1, 2, 4-14, 42, 43, and 60 are pending.

The specification is amended herein to capitalize trademarks on pages 12, 13, 17, 25, 27, and 28, and to correct a typographical error on page 21. In addition, a replacement Sequence Listing is submitted herewith. Applicant requests that the replacement Sequence Listing be entered in the application. In the replacement, the organisms for SEQ ID NOS:3, 4, 5, and 6 are corrected, since their labels as mouse or human sequences were inadvertently interchanged in the previous submission.

Claim 1 is amended herein to recite a purified variant costimulatory polypeptide, wherein said variant polypeptide is a variant of a wild-type costimulatory polypeptide that binds to PD-1, wherein the wild-type costimulatory polypeptide has the amino acid sequence set forth in SEQ ID NO:3 or SEQ ID NO:4, wherein the variant costimulatory polypeptide has binding affinity for PD-1 that is detectable by ELISA but is reduced by at least 50 percent as compared to the binding affinity of the wild-type costimulatory polypeptide for PD-1, and wherein the variant costimulatory polypeptide retains the ability to costimulate a T cell. New claim 60 depends from claim 1, and recites that the binding affinity of the variant polypeptide for PD-1 is reduced by at least 50 percent but not more than 98.6 percent as compared to the binding affinity of the wild-type costimulatory polypeptide for PD-1. These amendments are fully supported by Applicant's specification. For example, Applicant's specification discloses that SEQ ID NOS:3 and 4 are the human and mouse B7-H1 sequences, respectively. *See*, e.g., page 7, lines 9-12. The specification also discloses variant B7-H1 polypeptides that have binding affinity for PD-1 that is detectable by ELISA, but is reduced as compared to a wild type B7-H1 polypeptide. As disclosed in Table 1 at page 30, for example, the observed reduction in binding affinity ranged from 40% to 98.6%, with intermediate values of 50%, 60%, 65%, 70%, 95%, 97%, and 98%. In addition, Applicant's specification discloses that variant B7-H1 polypeptides retained the ability to costimulate T cells. *See*, e.g., page 32, line 20 to page 33, line 8, as well as Figures 11 and 12.

In addition, claims 42 and 43 are amended herein to recite a "polypeptide fragment" throughout, and to recite that the polypeptide fragment comprises a variant with respect to the sequence set forth in SEQ ID NO:4, wherein the variant is at position 69 or 113 with respect to SEQ ID NO:4. Support for these amendments can be found in Applicant's specification at, for example, Table 1 on page 30, which discloses that B7-H1 polypeptides containing variants at positions 69 and 113 had increased binding to PD-1. Thus, no new matter has been added.

In light of these amendments and the following remarks, Applicant respectfully requests reconsideration and allowance of claims 1, 2, 4-14, 42, 43, and 60.

Sequence listing

The Examiner stated that the application does not comply with the requirements of 37 C.F.R. §§ 1.821-1.825, because the sequences disclosed at least in Figure 9 are not accompanied by sequence identifiers. Applicants respectfully note that the sequences shown in Figure 9 are contiguous across multiple lines. That is, SEQ ID NO:11, which is a CD86 sequence, begins as the top line of the top group of sequences, continues as the top line of the second group of sequences, and finishes as the top line of the third group of sequences. Likewise, SEQ ID NO:12, which is a CD80 sequence, is a contiguous sequence set forth as the second line of the top, middle, and bottom groups of sequences. Thus, all sequences are accompanied by sequence identifiers.

In light of the above, Applicant submits that the present application is in compliance with 37 C.F.R. §§ 1.821-1.825.

Title

The Examiner stated that the title of the application is not descriptive of the invention to which the claims are directed. Applicant has amended the title herein to remove the reference to B7-DC. Thus, the title is descriptive of the invention to which the claims are directed.

Trademarks

The Examiner noted that each letter of a trademark in a patent application should be capitalized. Applicant has amended the specification at pages 12, 13, 17, 25, 27, and 28 to capitalize the trademarks included therein.

Rejections under 35 U.S.C. § 112

The Examiner rejected claims 1-14, 42, and 43 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. The Examiner asserted that claims 1-14 are indefinite in the recitation of "substantial costimulatory activity," because the metes and bounds of the recitation are unclear. Specifically, the Examiner alleged that the term "substantial" is a relative term. The Examiner also alleged that costimulation is a complex, multifaceted process, and that it is not clear which aspects of costimulation are encompassed in the recitation of "costimulator activity." The Examiner further asserted that claims 42 and 43 are indefinite in the recitation of "said polypeptide," because the phrase lacks antecedent basis in the preceding part of the claim.

To further prosecution, Applicant has amended claims 42 and 43 to consistently recite a polypeptide fragment. In addition, Applicant has amended claim 1 to recite that the variant costimulatory polypeptide retains the ability to costimulate a T cell. A person of ordinary skill in the art reading Applicant's specification at the time of filing would have understood the metes and bounds of this recitation. This is particularly true given that Applicant's specification discloses that a "costimulatory polypeptide" is a polypeptide that, upon interaction with a cell-surface molecule on a T cell, enhances a T cell response (e.g., stimulates T cell proliferation and/or cytokine release). *See*, e.g., page 9, lines 7-9. Applicant's specification further discloses that variant B7-H1 polypeptides were able to costimulate T cell proliferation and interferon production. *See*, e.g., page 32, lines 20-30. Thus, the present claims are clear and definite.

In light of the above, Applicant respectfully requests withdrawal of the rejection of claims 1, 2, 4-14, 42, and 43 under 35 U.S.C. § 112, second paragraph.

The Examiner rejected claims 42 and 43 under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement. The Examiner stated that the specification does not appear to provide a sufficient enabling description of polypeptide fragments comprising the specified amino acids of SEQ ID NO:4, wherein the fragments inhibit binding of murine B7-H1 to murine PD-1. The Examiner further asserted that the specification does not appear to provide sufficient guidance as to which subsequences of SEQ ID NO:4 share the presumed ability of the full-length SEQ ID NO:4 polypeptide, nor does it appear to provide adequate working examples of such functional fragments. In addition, the Examiner noted that the term "comprising" in claims 42 and 43 is open-ended, and thus, the Examiner concluded that undue experimentation would be required for one of ordinary skill in the art to determine which polypeptide sequences encompassed by the instant claims would share the function of SEQ ID NO:4.

Applicant respectfully disagrees. Amended claims 42 and 43 recite a polypeptide fragment of murine B7-H1 (SEQ ID NO:4) comprising amino acids 67-69 or 113-115 of SEQ ID NO:4, wherein the polypeptide fragment inhibits binding of murine B7-H1 to murine PD-1, and wherein the polypeptide fragment comprises a variant at position 69 or 113 with respect to SEQ ID NO:4. Thus, the recited fragment is a fragment of SEQ ID NO:4. A person of ordinary skill in the art reading Applicant's specification at the time of filing would readily have been able to make and use the presently claimed polypeptide fragments. This is particularly true given that (1) methods for producing polypeptides were routine in the art at the time Applicant filed, (2) the level of skill in the art at the time of filing was quite high, and (3) Applicant's specification teaches how to make and use the recited fragments. In particular, the specification provides the amino acid sequence of SEQ ID NO:4 from which the recited fragments are derived (*see*, Figure 2). The specification also teaches methods for making (e.g., by chemical synthesis or by recombinant production) and purifying polypeptides and polypeptide fragments. *See*, e.g., page 12, line 1 to page 13, line 23. In addition, Applicant's specification teaches *in vitro* and *in vivo* methods for testing the ability of a polypeptide or polypeptide fragment to bind PD-1 and for using a polypeptide or polypeptide fragment to inhibit interaction of B7-H1 with PD-1. *See*, e.g., the section extending from page 17, line 29 to page 24, line 12, and in particular the section extending from page 23, line 30 to page 24, line 12. *See*, also, the methods disclosed at page 26, line 20 to page 28, line 15. In addition, Applicant respectfully directs the Examiner to *In re Wands* (858 F.2d 731 (C.A.Fed. 1988)), in which the court stated that "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed" (citing *In re Jackson*, 217 USPQ at 807 ((Bd. App. 1982)). Given the guidance provided by Applicant's specification and the level of skill in the art, no undue experimentation would have been required for one of ordinary skill to make the recited polypeptide fragments of SEQ ID NO:4, and to determine which fragments have the recited function. Thus, the present claims are fully enabled.

In light of the above, Applicant respectfully requests withdrawal of the rejection of claims 42 and 43 under 35 U.S.C. § 112, first paragraph.

Rejections under 35 U.S.C. § 102

The Examiner rejected claims 1-4 under 35 U.S.C. § 102(b) as allegedly being anticipated by U.S. Patent No. 5,580,756 (the Linsley *et al.* patent). The Examiner stated that the Linsley *et al.* patent discloses costimulatory polypeptide B7, which shares a "limited degree" of sequence homology with B7-H1. As such, the Examiner asserted that the disclosed B7 polypeptide represents a "variant of a wild-type costimulatory polypeptide that binds PD-1." The Examiner further alleged that one of skill in the art would have been aware that "B7/CD80 does not detectably bind PD-1, and thus 'has reduced binding affinity for PD-1 as compared to wild-type [B7-H1].'"

Applicant respectfully disagrees. While the Examiner correctly noted that there is a "limited degree" of sequence homology between B7 and B7-H1, a sequence alignment and comparison performed using the Blast 2 Sequences program available at the NCBI Blast web site (http://www.ncbi.nlm.nih.gov/BLAST/) reveals that there is actually only about 23% sequence identity between the two proteins. Further, that limited identity is observed only over a stretch of 191 amino acids, whereas the full length B7-H1 protein is 290 amino acids in length. Thus, Applicant respectfully submits that it is a stretch to state that B7 is a variant of B7-H1.

Nevertheless, to further prosecution Applicant has amended claim 1 to recite that the variant costimulatory polypeptide has binding affinity for PD-1 that is detectable by ELISA but is reduced by at least 50 percent as compared to the binding affinity of the wild-type costimulatory polypeptide for PD-1. The Linsley *et al.* patent does not disclose such a polypeptide since, as noted by the examiner, B7 does not have detectable binding to PD-1. Thus, the Linsley *et al.* patent does not anticipate the presently claimed polypeptides.

In light of the above, Applicant respectfully requests withdrawal of the rejection of claims 1-4 under 35 U.S.C. § 102(b).

The Examiner rejected claims 42 and 43 under 35 U.S.C. § 102(a) as allegedly being anticipated by U.S. Publication No. 2002/0102651 (the Freeman *et al.* publication). The Examiner asserted that the Freeman *et al.* publication discloses B7-4, which is an alternative name of the instantly claimed B7-H1, and fragments thereof. The Examiner alleged that the full-length B7-4 polypeptide inherently comprises any fragment of the same polypeptide, including those fragments comprising the specific amino acids recited in claims 42 and 43.

To further prosecution, Applicant has amended claim 42 to recite a polypeptide fragment of murine B7-H1 (SEQ ID NO:4), the polypeptide fragment comprising amino acids 67-69 or amino acids 113-115 of SEQ ID NO:4, wherein the polypeptide fragment comprises a variant with respect to the sequence set forth in SEQ ID NO:4, wherein the variant is at position 69 or 113 with respect to SEQ ID NO:4, and wherein the polypeptide fragment inhibits binding of murine B7-H1 to murine PD-1. The Freeman *et al.* publication does not disclose the presently claimed polypeptide fragments. For example, at no point does the Freeman *et al.* publication disclose a fragment of the mouse sequence set forth in SEQ ID NO:4 that contains a variant at position 69 or position 113 with respect to SEQ ID NO:4. Thus, this reference does not anticipate the present claims.

In light of the above, Applicant respectfully requests withdrawal of the rejection of claims 42 and 43 under 35 U.S.C. § 102(a).

Double patenting rejection

The Examiner provisionally rejected claims 42 and 43 as being unpatentable over claim 36 of copending application Serial No. 10/890,789 (the '789 application). The Examiner alleged that because the claims of both applications are drawn to proteins comprising fragments of B7-H1, the conflicting claims are not patentably distinct.

Applicant respectfully disagrees. Claim 36 of the '789 application recites a fusion protein comprising a first domain joined to at least one additional domain, wherein the first domain comprises a polypeptide encoded by a DNA comprising: (i) a nucleic acid sequence that encodes a polypeptide with the ability to co-stimulate a T cell, wherein the nucleic acid sequence hybridizes under stringent conditions to the complement of a sequence that encodes a polypeptide with an amino acid sequence with SEQ ID NO:1 or SEQ ID NO:3; or (ii) the complement of the nucleic acid sequence. Present claims 42 and 43 recite a polypeptide fragment of murine B7-H1 (SEQ ID NO:4), the polypeptide fragment comprising amino acids 67-69 or amino acids 113-115 of SEQ ID NO:4, wherein the polypeptide fragment comprises a variant at position 69 or position 113 with respect to the sequence set forth in SEQ ID NO:4, and wherein the polypeptide fragment inhibits binding of murine B7-H1 to murine PD-1. Present claims 42 and 43 do not recite a fusion protein per se, nor do they recite a polypeptide that is required to have the ability to costimulate a T cell. Further, claim 36 of the '789 application does not recite a fragment of murine B7-H1, much less a fragment of murine B7-H1 having a variant at position 69 or 113 with respect to SEQ ID NO:4, nor does it recite that the fusion protein inhibits binding of murine B7-H1 to PD-1. Thus, the polypeptide fragment recited in present claims 42 and 43 is not an obvious variant of the fusion protein recited in claim 36 of the '789 application. As such, a double patenting rejection is not warranted.

In light of the above, Applicant respectfully requests withdrawal of the provisional rejection of claims 42 and 43 for obviousness-type double patenting.

CONCLUSION

Applicant submits that claims 1, 2, 4-14, 42, 43, and 60 are in condition for allowance, which action is respectfully requested. The Examiner is invited to telephone the undersigned agent if such would further prosecution.

Please charge $60 for the Petition for Extension of Time fee, and apply any other charges or credits, to deposit account 06-1050.

Respectfully submitted,

Date: July 21, 2006

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